



Express Mail No. EV780368135US  
Date of Deposit: March 30, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Guenther, Catherine	Examiner:	Wilson, Michael C.
Serial No.:	09/883,093	Group Art Unit:	1632
Filed:	June 14, 2001	Docket No.:	R126/75658.241
Confirmation No.:	7936		
Title:	Transgenic Mice Containing Nuclear Hormone Receptor Gene Disruptions		

**DECLARATION OF JOHN BURKE PURSUANT TO 37 C.F.R. § 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, John E. Burke, residing at 16357 E. Berry Avenue, Centennial CO 80015, hereby declare:

1. I am currently, and have been since 1998, the Attorney of Record for the Applicant and Assignee, Deltagen, Inc. I am listed on the originally filed Power of Attorney for the present application. From December 1996 to December 1999, I was Of Counsel with the law firm of Pillsbury Madison & Sutro (currently Pillsbury Winthrop) where I represented Deltagen with respect to intellectual property matters, including patent matters relating to their transgenic mouse program. From December 1999 until December 2001, I served as Deltagen's Vice President of Intellectual Property, where I supervised Deltagen's internal patent department. All of the applications, including the present application, covering the 750 lines of mice in DeltaBase were drafted by Deltagen's patent department. From December 2001 until April 2003, I served as Deltagen's Senior Vice President and General Counsel. From April 2003 through April 2005, I was a partner with the Denver office of Merchant & Gould, where I continued to represent Deltagen with regard to intellectual matters, including patent matters. I am presently employed as a Shareholder with the Denver office of the law firm of Greenberg Traurig, where I am

responsible for prosecution of Deltagens's patent portfolio relating to their transgenic mice program, including the present application.

2. I am familiar with the present application. I am familiar with the Final Office Action mailed October 6, 2005. I am aware that the Examiner has rejected the claims, in part, for allegedly failing to meet the utility and enablement requirements. I am aware that the Examiner has argued that the specification does not disclose what generation mice were used or what wild-type controls were used in the phenotypic analyses.

3. I hereby declare that, as evidenced by the attached Exhibit, the subject matter of the present application, mCAR2 gene knockout mice, were compared with control mice of identical background.

4. I hereby declare that the claimed mCAR2 gene knockout mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase.

5. I hereby declare that I have accessed Deltagen's internal web-based DeltaBase database to review the data derived from analyses of the claimed mice. I hereby declare that the attached Exhibit contains three (3) pages, representing screen printouts from DeltaBase.

6. Exhibit pages 1 and 2 represent a series of screen shots of the Histopathology Summary for the mCAR2 gene. As shown, the mCAR2 gene has been internally designated as Gene 126. The Accession number is referred to at the top of the page (AF009328). According to the Summary, changes that may be related to genotype include lymphoid depletion of the thymus. The Summary further notes that the "changes seen in the thymuses of affected animals are suggestive of thymic dysplasia; however, severe atrophy cannot be ruled out."

7. Exhibit page 3 shows the raw histopathology data, and more specifically, the recorded observations for the thymus. Column 1 indicates the gene number 126; column 2 indicates the

ES cell line 200; column 3 indicates the genotype; column 4 indicates the sex of the subject mouse and column 6 indicates the mouse ID number. All of the mice are of the same generation, F2N0. Thus, the homozygous (-/-), heterozygous (+/-) and wild type mice (+/+) were derived from the same ES cell line, and are of the same F and N generation. Thus, the mice were compared with mice of the same background.

8. I further declare that all statements made herein of my own knowledge are true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

  
\_\_\_\_\_  
John E. Burke, Reg. No. 35,836

3-30-06  
\_\_\_\_\_  
Date

DeltaBase - Microsoft Internet Explorer provided by Greenberg Traurig

Address: https://delweb.deltagen.com/deltabase\_web/Main.asp?Data=Summaries%2FTargetSummaryProgramLinksDisplay%2Easp&ActiveTab=4%2C9

Current User: JBURKE

gene: **organ system** **hot hits**

126 Nuclear Hormone  
131 Nuclear Hormone  
134 Cell Adhesion  
136 Cell Adhesion  
137 Protease  
140 Protease  
142 Protease  
143 Protease  
150 Growth Factor  
158 Channel  
159 Channel  
160 Channel  
171 GPCR  
172 GPCR  
174 GPCR

Gene 126  
Histopathology

Last Modified By: Solano, Zendi  
Last Modified On: 7/2/2002 3:44:58 PM

Changes related to genotype:

- Spleen, lymphoid depletion, minimal to moderate.
- Thymus, lymphoid depletion, minimal to severe.
- Lymph nodes, possible lymphoid depletion, pending additional studies.

Tissues from the mice listed below were evaluated histologically.

49 Day Cohort Mouse ID numbers are as follows:

- 3 homozygous mutant females (15116, 15135, 15470)
- 3 homozygous mutant males (15105, 15112, 30903)
- 2 heterozygous mutant females (15118, 15469)
- 1 heterozygous mutant male (15110)
- 2 wild-type control females (15134, 15471)
- 2 wild-type control males (15102, 15111)

300 Day Cohort Mouse ID numbers are as follows:

- 2 homozygous mutant females (22194, 22993)
- 3 homozygous mutant males (19464, 22179, 28046)

Mice							
#	Sex	Genotype	I Gen	H Gen	Age	Validity	Release
15116	Female	-/-	2	0	50	V	T
15135	Female	-/-	2	0	50	V	T
15470	Female	-/-	2	0	47	V	T
22194	Female	-/-	2	0	307	V	T
22993	Female	-/-	2	0	306	V	T
15105	Male	-/-	2	0	52	V	T
15112	Male	-/-	2	0	50	V	T
19464	Male	-/-	2	0	327	V	T
22179	Male	-/-	2	0	307	V	T
28046	Male	-/-	2	0	304	V	T
30903	Male	-/-	2	0	50	V	T
15110	Female	+/+	2	0	50	V	T
15469	Female	+/+	2	0	47	V	T
15110	Male	+/+	2	0	50	V	T
15134	Female	+/+	2	0	50	V	T
15471	Female	+/+	2	0	47	V	T
22193	Female	+/+	2	0	307	V	T
22995	Female	+/+	2	0	306	V	T
15102	Male	+/+	2	0	52	V	T
15111	Male	+/+	2	0	50	V	T

EXPRESSON ANAL  
PATHOLOGY  
MICROPSY  
Data →  
Graph: Ave.  
Weight →  
Macropsy  
weights →  
Images →  
Graph: Ave.  
Wt. Body Wgt. →  
HISTOPATHOLOGY  
Data →  
Images →  
HEMATOLOGY  
SERUM CHEMISTRY

DeltaBase - Microsoft Internet Explorer provided by Greenberg Traurig

Address: https://delweb.deltagen.com/deltabase\_web/Main.asp?Data=Summaries%2FTargetSummaryProgramLinksDisplay%2Easp&ActiveTab=4%2C9

Current User: JBURKE

gene: **organ system** **hot hits**

126 Nuclear Hormone  
131 Nuclear Hormone  
134 Cell Adhesion  
136 Cell Adhesion  
137 Protease  
140 Protease  
142 Protease  
143 Protease  
150 Growth Factor  
158 Channel  
159 Channel  
160 Channel  
171 GPCR  
172 GPCR  
174 GPCR

3 homozygous mutant males (19464, 22179, 28046)  
2 wild-type control females (22193, 22995)  
3 wild-type control males (19350, 22182, 28047)

Histopathology Findings:

At 49 days, four of the eight mutant mice examined have splenic and thymic lymphoid depletion: one homozygous male (15112), one heterozygous male (15110), and two homozygous females (15116, 15135). Lymphoid depletion in the spleen appears to involve lymphocytes in the periarteriolar lymphoid sheaths, however immunoperoxidase stains are needed to more definitively compartmentalize this lesion. In the thymus, there is a reduction in the number of cortical lymphocytes. Two additional animals have minimal lymphoid depletion in the spleen with no changes seen in the thymus (15105 homozygous male, 15118 heterozygous female).

Lymph nodes from the affected animals are reduced in size. In the few nodes available for evaluation, there may be a reduction lymphocytes; however immunohistochemistry is necessary to further define these changes.

The changes seen in the thymuses of affected animals are suggestive of thymic dysplasia; however, severe atrophy cannot be ruled out. Thymic dysplasia, a congenital lesion associated with T cell immunodeficiency, consists variable degrees of the following features: a dramatic reduction in size of the thymus, a foliated appearance of the gland, depletion of lymphoid cells, and a lack of

15111	Male	+/+	2	0	50	V	T
19350	Male	+/+	2	0	329	V	T
22182	Male	+/+	2	0	307	V	T
28047	Male	+/+	2	0	304	V	T

EXPRESSON ANAL  
PATHOLOGY  
MICROPSY  
Data →  
Graph: Ave.  
Weight →  
Macropsy  
weights →  
Images →  
Graph: Ave.  
Wt. Body Wgt. →  
HISTOPATHOLOGY  
Data →  
Images →  
HEMATOLOGY  
SERUM CHEMISTRY

DeltaBase - Microsoft Internet Explorer provided by Greenberg Traurig

Address: https://deltaweb.deltagen.com/deltabase\_web/Main.asp?Data=Summaries%2FTargetSummaryProgramLinksDisplay%2Easp&ActiveTab=4%2C9

DeltaBase™ **Summaries** **data** **onlinehelp** **logout** Current User: JBURKE

gene organ system hot hits

126 Nuclear Hormone  
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134 Cell Adhesion  
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137 Protease  
140 Protease  
142 Protease  
143 Protease  
150 Growth Factor  
158 Channel  
159 Channel  
160 Channel  
171 GPCR  
172 GPCR  
174 GPCR

Target: 126 Nuclear Hormone  
Accession: AB010000  
GI: 2267577  
External Link: Select External Database

foliated appearance of the gland, depletion of lymphoid cells, and a lack of maturation of epithelial cells which appear primitive and fail to properly differentiate into Hassall's corpuscles. Thymic dysplasia is believed to represent a failure or arrest in the embryological development of the gland. Atrophic changes of the thymus are acquired and can be induced by stress-related adrenocortical hyperactivity, decreased levels of growth hormone, and direct toxicity. Dysplasia and severe atrophy can be distinguished by cytokeratin and T cell specific Immunohistochemistry stains.

At 300 days, two homozygous animals have thymic lymphoid depletion (male 22179, female 22194). There were no significant pathologic abnormalities in the spleens or lymph nodes in the animals in this study.

**EXPRESSION ANAL.**  
**PATHOLOGY**  
**NECROPSY**  
Data →  
Graph: Ave.  
Weight →  
Meatcopy  
weights →  
Images →  
Graph: Ave.  
Wgt./Body Wgt. →  
**HISTOPATHOLOGY**  
Data →  
Images →  
**HEMATOLOGY**  
**SERUM CHEMISTRY**

No Significant Abnormalities:

Tissues examined and considered histologically normal (no significant abnormality) except as specifically noted above: brain, pituitary gland, salivary glands, lymph nodes, aorta, lungs, gallbladder, pancreas, spleen, kidneys, urinary bladder, stomach, small and large intestines, larynx, esophagus, trachea, thyroid gland, tongue, skeletal muscle, sciatic nerve, skin, mammary gland, vertebrae, spinal cord, bone (cranium, sternum, femur, tibia, and stifle joint), reproductive tract including gonads, eyes, and Harderian glands.

Bone marrow was evaluated in sections of sternum, vertebrae, and/or femur

Done! Internet

